Cancer patients requiring interruption of long-term warfarin because of surgery or chemotherapy induced thrombocytopenia: The use of fixed sub-therapeutic doses of low-molecular weight heparin

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No data are available regarding the management of cancer patients requiring interruption of long-term vitamin-K antagonist (VKA) therapy. For this purpose, we tested the efficacy and safety of fixed doses of low-molecular weight heparin (LMWH) in substitution of VKA because of invasive procedures or chemotherapy-induced thrombocytopenia. In cancer patients on VKA, therapy was discontinued 5 ± 1 days before surgery or chemotherapy. Heparin was given at prophylactic dosage in patients at low risk and at fixed subtherapeutic doses (3,800 or 4,000 UI anti-FXa, b.i.d.) in those at high-risk for thrombosis. LMWH was reinitiated 12 hr after surgery and VKA the day after. In patients receiving chemotherapy, LMWH was reinitiated 12/24 hr after obtaining a stable platelet count $\geq$ 30,000 mmc^3 and VKA after a stable platelet count $\geq$ 50,000 mmc^3. Thromboembolism and major bleeding events were recorded from the time of VKA suspension to 30 ± 2 days postprocedure or until the next chemotherapy. Overall, 156 patients (56.4% at low risk and 43.5% at high risk for thrombosis) were enrolled; 34.6% underwent major surgery, 40.4% nonmajor surgery, and 25% chemotherapy. Thrombotic events occurred in five patients [3.2%, 95% confidence interval (CI): 1.41–7.27], four belonging to the high-risk and one to the low-risk group. Major bleeding occurred in five patients (3.2%, 95 CI: 1.41–7.27), all belonging to the high-risk group (three during major surgery and two during chemotherapy). In conclusion, LMWH given at fixed subtherapeutic is a feasible and relatively safe approach for bridging therapy in cancer patients on long-term VKA. Am. J. Hematol. 87:388–391, 2012. © 2012 Wiley Periodicals, Inc.

Introduction

Cancer patients receiving long-term vitamin-K antagonist (VKA) therapy pose a clinical challenge when anticoagulant therapy needs to be interrupted for surgical/invasive procedures or chemotherapy-induced thrombocytopenia [1]. Interruption of anticoagulant therapy exposes patients to an increased risk of thromboembolic events (TE) (i.e., stroke or mechanical valve thrombosis), although such a risk varies depending on the indication for the antithrombotic therapy and on the presence of comorbid conditions [2]. Conversely, the administration of anticoagulants during surgical procedures increases the risk of major bleeding. To manage such situations, two options are available. The first strategy is to continue oral anticoagulation therapy with a temporary adjustment of warfarin intensity to a preoperative international normalized ratio (INR) of 1.5–2.0. However, such an approach is associated with a high rate of bleeding in noncancer patients [3]. Another strategy involves switching VKA to low-molecular weight heparin (LMWH; so-called bridging therapy) some days before the procedure, at doses and timings related to the individual thrombotic burden as well as their bleeding risk due to the procedure. This last approach has been proven to reduce the thrombotic risk without increasing the occurrence of periprocedural major bleeding [4–8]. However, in none of the prospective studies evaluating the safety of "bridging therapy" it is possible to extrapolate data on the cancer population.

Cancer patients are a high-risk population both for thrombosis and bleeding [9]; moreover, cancer-related therapy may decrease platelet count, thus increasing the risk for periprocedural bleeding [10–12]. Therefore, the use of anticoagulation in such a population may be difficult and requires appropriate investigation.

For this purpose, we prospectively tested the use of fixed subtherapeutic doses of LMWH as a bridging therapy in cancer patients on long-term VKA requiring the suspension of anticoagulation because of an expected high risk of bleeding during surgery or other invasive procedures or from chemotherapy-induced thrombocytopenia.

Materials and Methods

Patient population. This was a prospective, cohort study evaluating the feasibility and safety of subcutaneous LMWH, administered primarily at home, in cancer patients on long-term VKA therapy for whom bridging therapy with heparin was planned because of exposure to procedures carrying the potential risk of bleeding. The study was conducted between 2005 and 2010 at the University Hospital of Palermo, Italy. The primary aim was to determine the incidence of periprocedural thromboembolic events and major bleeding during the administration of bridging anticoagulation over the 30 days following surgery.

Inclusion criteria included consecutive adult cancer patients requiring long-term VKA therapy for mechanical heart valves, patients with atrial fibrillation (AF), stroke with an embolic source, venous thromboembolism (VTE), or other indications (Table I) planned for any procedure requiring the interruption of VKA (as listed above) or chemotherapy-induced thrombocytopenia. Patients were excluded for the following reasons: plans to undergo minor surgery or a simple dental procedure, renal insufficiency (serum creatinine $>$ 2.0 mg/dL), previous major bleeding episode (i.e., haemorrhagic stroke), chronic anaemia (haemo-

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Conflict of interest: Nothing to report

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TABLE I. Baseline Characteristics

Patients characteristics (n = 156)	
Mean age (range, years)	66.6 (32/89)
M/F (%)	84/72
Weight, mean ± SD (kg)	75.4 ± 16.5
Solid cancer, *n* (%)	98 (62.8)
Haematological cancer, *n* (%)	58 (37.2)
Advanced/metastatic cancer, *n* (%)	101 (64.7)
Bridging therapy with nadroparin, *n* (%)	71 (45.5)
Bridging therapy with enoxaparin, *n* (%)	79 (50.6)
Bridging therapy with others heparin compounds, *n* (%)	6 (3.8)
Low-risk for TE	88 (56.4)
Patients on chemotherapy-induced thrombocytopenia	22[a]
High-risk for TE	68 (43.5)
Patients on chemotherapy-induced thrombocytopenia	17[b]
Venous thromboembolism, *n* (%)	52 (33.3)
Events lasting < 3 months, *n* (%)	28
Events lasting > 3 months, *n* (%)	24
Atrial fibrillation without previous stroke (AF-NoAT), *n* (%)	48 (30.7)
Atrial fibrillation with previous stroke (AF-AT), *n* (%)	21 (13.4)
Prosthetic aortic/mitral valves, *n* (%)	19 (12.1)
Others (arterial hypertension, dilatative myocardiopathy, valvulopathy, myocardial infarction, coronary artery by-pass graft), *n* (%)	16 (10.2)

[a] 16 (72.7%) had haematological malignancies.
[b] 11 (64.7%) had haematological malignancies.

globin $\leq$ 10 g/L), or persistently low-platelet count ($<$100,000 per mm^3) not related to chemotherapy, severe associated pathologies (i.e., uncontrolled hypertension or diabetes and severe hepatic failure), pregnancy, anticoagulant therapy other than warfarin or acenocoumarol, or when body weight $\leq$ 40 kg or $\geq$ 100 kg. Patients with known sensitivities to pork products, murine proteins, UFH, or LMWH or any of its constituents, or a history of heparin-induced thrombocytopenia were also excluded. Procedures were categorized as major (any operation with an expected duration $\geq$ 1 hr), nonmajor surgery (invasive procedures lasting $\leq$ 1 hr, such as gastro- or colonoscopy requiring biopsy), or chemotherapy-induced thrombocytopenia.

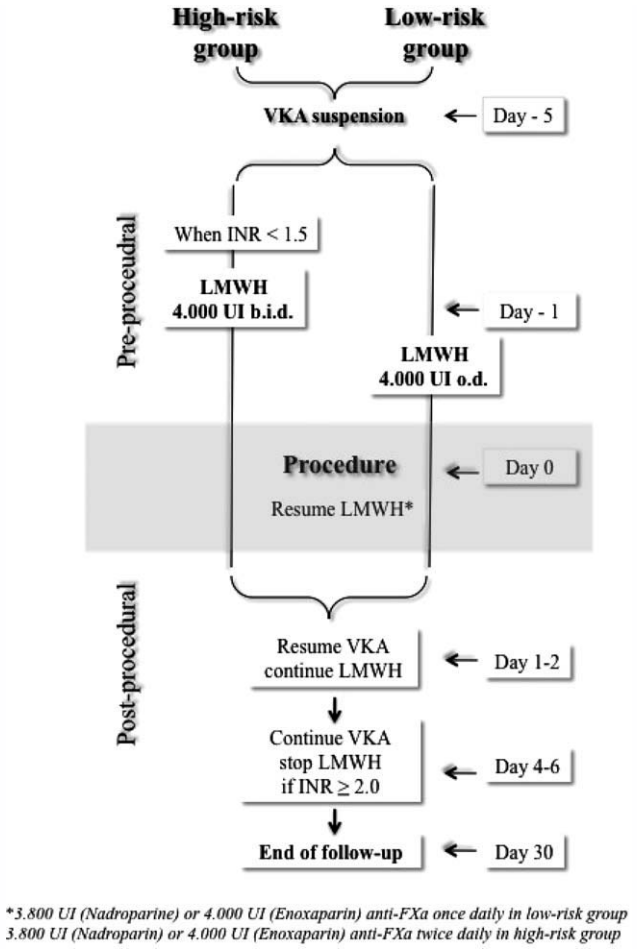

Figure 1. Study protocol.

Study Design

The periprocedural management of anticoagulation is outlined in Fig. 1. Patients were categorized as being at a low or high risk of thrombosis. The first group included patients suffering with AF with no previous arterial thromboembolism (TE; AF-noAT), VTE lasting more than 3 months, those with prosthetic aortic valves, or another indication (Table I). The high-risk group included patients with AF with previous arterial TE (AF-AT), prosthetic mitral valves, or those with recent VTE (lasting $\leq$ 3 months).

Preprocedural management

In all patients, VKA was discontinued 5 ± 1 days before the procedure. In patients considered to be at a low risk of thrombosis (low-risk group), LMWH was initiated once daily at a prophylactic dosage (3,800 or 4,000 U.I. anti-FXa according to the use of nadroparin or enoxaparin, respectively), the night before the procedure. In patients considered to be at a high risk of thrombosis (high-risk group), the INR was checked daily preoperatively; when an INR value $\leq$ 1.5 was obtained, LMWH was initiated twice daily at a fixed subtherapeutic dose (3,800 or 4,000 U.I. anti-FXa according to the use of nadroparin or enoxaparin, respectively) and continued until the night before the procedure.

Postprocedural management

Twelve hours after the procedure, LMWH was given at a prophylactic dose in the low-risk group and at a fixed subtherapeutic dose in the high-risk group (as reported above). VKA was restarted the day after the procedure or later in the case of inadequate haemostasis; the dose of warfarin was the same as the patient's usual daily dose. Heparin was continued until the INR value fell within a therapeutic range. The physician had the option of delaying the first postprocedural LMWH in cases where there was an increased risk of bleeding. Hemoglobin and platelet levels were measured every 1–2 days while patients were on LMWH. The INR was measured every 1–2 days during the first week after the procedure. The follow-up period extended from the day of the procedure to about 1 month (30 ± 2 days) thereafter.

In patients who experienced chemotherapy-induced thrombocytopenia, VKA was discontinued 5 ± 1 days before chemotherapy, and LMWH therapy was commenced the day after (following the same scheme reported above, according to the risk-group). Heparin was discontinued when the platelet count dropped to less than 30,000 mmc^3; LMWH was reinitiated 12–24 hr after a stable platelet count $\geq$ 30,000 mmc^3 was reached, and VKA was reinitiated 12–24 h after reaching a stable platelet count $\geq$ 50,000 mmc^3. Heparin was continued until the INR value fell within a therapeutic range.

Patients were screened within 30 ± 2 days following the procedure or chemotherapy for any potential signs or symptoms suggestive of thrombosis and/or bleeding or any other serious medical condition.

Statistics and Ethics

The intention-to-treat (ITT) study population was defined as all patients who received at least one dose of LMWH. All analyses were performed on this population. Baseline patient characteristics and the periprocedural anticoagulation regimen were expressed as mean values with corresponding standard deviations. Clinical outcome rates (recurrent TE,

TABLE II. Thromboembolic Events in the Low-Risk, High-Risk, and Total Patient Groups

Events, *n* (%)	Low-risk group (68)	High-risk group (88)	Total (156)	*P* value among low and high-risk group[a]
TE total, *n* (%, 95% CI)	1 (1.4, 95% CI: 0.35–7.81)	4[b] (4.5, 95% CI: 1.84–11.10)	5 (3.2, 95% CI: 1.41–7.27	0.387
Arterial, *n* (%, 95% CI)	0	1 (1.1, 95% CI: 0.27–6.10)	1 (0.6, 95% CI: 0.15–3.49)	1.0
Venous, *n* (%, 95% CI)	1 (1.4, 95% CI: 0.35–7.81)	3 (3.4, 95% CI: 1.23–9.53)	4 (2.5, 95% CI: 1.04–6.39)	0.632

[a] Fisher's exact test.

[b] One event occurred in this group during chemotherapy-induced thrombocytopenia.

Abbreviations: TE, thromboembolism; AF-AT, atrial fibrillation with previous stroke; VTE, venous thromboembolism; CI, confidence interval.

TABLE III. Incidence of Major Bleeding Events in the Low and High-Risk Groups Accordingly to Type of Procedure

Type of procedure (*n*)	Low-risk group	High-risk group
Major surgery (54) *n* (%, 95% CI)	0	3 (5.5, 95% CI: 2.0–15.1)
Non-major surgery (63) *n* (%, 95% CI)	0	0
Chemotherapy-induced thrombocytopenia (49) *n* (%, 95% CI)	0	2 (4.1, 95% CI: 1.2–13.7)

CI, confidence interval.

bleeding, and death) were expressed as a proportion with a corresponding upper 95% confidence interval (CI). Frequency analysis was performed using the Fisher's exact test suitable for small samples. Based on the incidence reported in previous published trials, we expected a 5% incidence of periprocedural major bleeding, thus giving a sample size of at least 150 patients (95% CI ± 1.5). The study protocol was reviewed and approved by the Institutional Review Board. Written formal consent was obtained from all patients enrolled in the study.

Outcome Assessments

Outcome of our investigation was the observed incidence of bleeding and thrombotic complications. We reported the incidence of any arterial or venous thromboembolic events occurring at any time during the study period (from VKA suspension to 30 ± 2 days thereafter). Arterial thromboembolic events were defined as ischaemic stroke documented by computed tomography (CT) scan or magnetic resonance imaging], transient ischaemic attacks (TIAs), peripheral arterial TE, or thrombosis of the prosthetic mechanical valves. Venous thromboembolic events were defined as acute symptomatic deep vein thrombosis (DVT), documented by compression ultrasound, or acute symptomatic pulmonary embolism (PE) documented by CT scan, pulmonary angiogram, or ventilation/perfusion scan. Arterial events that occurred in patients with no history of AF (i.e., enrolled because of a history of DVT) and venous events that occurred in patients with no history of DVT (i.e., enrolled because of a history of AF) were recorded and considered to be part of the primary efficacy endpoint.

We reported the incidence of major bleeding while on LMWH and during the follow-up period. Major haemorrhage was defined as overt bleeding leading to a $\geq$20 g/L drop in hemoglobin (compared to preoperative levels), transfusion of $\geq$2 U of packed red blood cells, any bleeding that was intracranial, retroperitoneal, or intraocular, requiring surgical intervention, or resulting in death. All suspected major bleeds were adjudicated by the study steering committee. The secondary safety outcome was the rate of minor bleeding while on LMWH or within 24 h after VKA discontinuation. All bleeding events not meeting the criteria for major bleeding were classified as minor.

Results

The study included 209 cancer patients on long-term anticoagulation therapy over a period of 5 years (2005–2010), investigated because of the need for invasive procedures, surgery or due to chemotherapy-induced thrombocytopenia. Among them, 44 were excluded (16 because of minor surgery or simple dental procedure, 4 because of renal insufficiency, 3 because of a previous major bleeding episode, 2 because of persistent low-platelet counts not related to chemotherapy, 14 because of severe associated pathologies, and 5 because of body weight $\leq$ 40 kg or $\geq$100 kg). In total, 165 patients were included in the study, 9 of which did not receive study medication. A total of 156 patients [88 (56.4%) at low risk and 68 (43.5%) at high risk of thrombosis] were enrolled. Eleven patients (7.0%) discontinued LMWH prematurely: eight for bleeding events, two for protocol violation (patients belonging to the high-risk group received prophylactic instead of subtherapeutic LMWH in the postprocedural period), and one lost during follow-up. These subjects were still considered part of the ITT population.

Baseline characteristics of the study population, as well as VKA indications, are shown in Table I. Among the 156 patients, 54 (34.6%) underwent major surgery, 63 (40.4%), nonmajor surgery, and 39 (25%), chemotherapy. Major surgery included the following procedures: 5 (9.2%) orthopedic, 16 (29.6%) abdominal, 8 (14.8%) urologic, 5 (9.2%) thoracic/lung, 8 (14.8%) gynaecologic, 11 (20.3%) mammary, and 3 (5.5%) neurosurgery. Nonmajor surgeries included 21 (33.3%) gastrointestinal endoscopies, 18 (28.5%) biopsies, 10 (15.8%) cutaneous surgeries, 11 (17.4%) urologic/gynaecologic (such as cystoscopies), and 3 (4.7%) arthroscopies.

The mean LMWH administration times (6.8 days) and the mean time required to reach a therapeutic INR level (5.6 days) were not different among low or high-risk patients either considering those underwent (major and nonmajor) surgery or chemotherapy-induced thrombocytopenia. Most patients undergoing nonmajor invasive procedures received LMWH at home, while the majority of patients planning to undergo major surgery or chemotherapy-induced thrombocytopenia received LMWH in the hospital.

Overall, thromboembolic events occurred in five patients (3.2%, 95% CI: 1.41–7.27), four belonging to the high-risk group (one during chemotherapy-induced thrombocytopenia) and one from the low-risk group. Three events (one TIA and two DVT) occurred in the AF-AT patient group, while two events (isolated PE and DVT with PE) occurred in the VTE patient group (Table II). All events occurred after surgery while patients were on anticoagulants, none of which were fatal.

Overall, major bleeding occurred in five patients (3.2%, 95 CI: 1.41–7.27), all belonging to the high-risk group (three during major surgery and two during chemotherapy; Table III). No bleeding event was fatal, intracranial, retroperitoneal, or intraocular. Four major bleeding events occurred during, or a few days after, major surgery, while one occurred in a patient undergoing chemotherapy. In patients who experienced bleeding events, LMWH was not administered, and VKA resumption was postponed until stable hemostasis was reached as determined clinically and by laboratory values.

In the group of patients who experienced chemotherapy-induced thrombocytopenia, the rate of thrombosis and major

bleeding was 2.0 (95% CI: 0.48–10.6) and 4.1% (95% CI: 1.2–13.7), respectively. The median nadir platelet count was 35.000 mmc^3 (range, 9.000–94.000 mmc^3); patients received platelet transfusions (by apheresis or randomly assigned) when platelets drop to $\leq$10.000 mmc^3 or with a platelet count of $\geq$10.000 – $\leq$50.000 mmc^3 in case of bleeding.

Minor bleedings occurred in 4 of 68 patients (5.9%, 95% CI: 2.39–14.2) in the low-risk group and 7/58 (12%, 95% CI: 6.0–22.9) in the high-risk group. Eight events occurred after VKA therapy was resumed. Three deaths occurred during the 30 days of follow-up, but none was related to major outcomes (recurrent thrombosis or major bleeding).

Discussion

The perioperative management of patients who require the temporary interruption of VKA is a common and challenging clinical problem. Physicians must balance the risk of thromboembolic events if VKA is discontinued with the risk of bleeding from the procedure if warfarin is continued. In a noncancer population, the 8th edition of *American College of Chest Physicians* states that patients on long-term VKA therapy at a high risk of thrombosis should receive bridging anticoagulation with a therapeutic-dose of s.c. LMWH or intravenous UFH during the temporary interruption of VKA therapy [1]. In patients at a moderate risk of TE, even a low dose of LMWH is allowed, while in patients at a low risk of TE, a low dose of LMWH is recommended. However, no data are available for a cancer population, a population at a high risk of thrombosis and bleeding.

For the first time in patients with active cancer, we evaluated a standardized bridging anticoagulation regimen with fixed doses of LMWH. In our series of 156 patients requiring the interruption of VKA because of invasive procedures, or due to chemotherapy-induced thrombocytopenia, our approach was associated with a relatively low risk of thromboembolic events (3.2%) and major haemorrhages (3.2%). As expected, major bleeding occurred more frequently in the group who underwent major surgery. After 30 days of follow-up, no patient died due to bleeding or thrombosis. These results are not different from those obtained in a noncancer population, where, using adjusted instead of fixed doses of LMWH, the rate of recurrent thrombosis and major bleeding ranged from 0.4 to 3.6% and from 1.2 to 20%, respectively [2–8]. As expected, we found a higher rate of events than those obtained in the noncancer population, using the same LMWH administration scheme. In this latter population, the rate of recurrent thrombosis and major bleeding was 1.8 and 2.1%, respectively [13]; however, a direct comparison is not easy to perform.

This cohort has several features that support the validity of the results. First, unlike most registries in which patient treatment is left to the discretion of the treating physician [14–16], patients received a standardized periprocedural anticoagulation regimen. This approach has several advantages. First, it simplifies the management of patients either pre- or postoperatively. Additionally, it is considered that the surgeon often feels uncomfortable, at least in our experience, giving therapeutic doses of heparin on the day immediately following surgery. This is particularly true in cases of chemotherapy-induced thrombocytopenia where no data are available concerning the platelet threshold considered safe for heparin administration, timing, and dosage. Finally, patients underwent a clinical follow-up during the preprocedural and postprocedural periods for up to 30 days, thus allowing us to detect any clinically relevant event.

There are some limitations that should be addressed. First, our study, similar to those in the noncancer population, lacked a comparison group. Without an untreated control group, we cannot determine whether such an approach reduced the incidence of TE or increased the frequency of bleeding. Only a randomized trial can address this clinical issue, but at present, none has been published. Second, our results come from a single-center investigation, and this may compromise data generalization. We cannot exclude such a hypothesis, but this appears unlikely, because the incidence of major events was similar to those reported in the noncancer populations evaluated in multicenter studies [2–8]. Finally, we excluded patients weighing $\leq$40 kg or $\geq$100 kg, which may reduce the generalization of our results; however, in our opinion, such patients should require an individualized protocol with bodyweight-adjusted doses of heparin.

In conclusion, the use of fixed doses of LMWH as a bridging regimen in cancer patients on long-term VKA is feasible and appears to be safe, because it is associated with a relatively low risk of recurrent thrombosis and major bleeding.

Author Contributions

Sergio Siragusa, Giorgia Saccullo, and Alessandra Malato designed the study protocol, analyzed the data, and wrote the paper. Giorgia Saccullo, Simona Raso, Marco Santoro, and Valentina Zammit performed the research and contributed to data analysis and manuscript revision. Alessandra Casuccio contributed to data analysis and statistics.

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